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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	M	ATTORNEY DOCKET NO.
08/307,540	09/16/94	FERGUSON		

HM11/0104

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EXAMINER	
CUNNINGHAM, T	

ART UNIT	PAPER NUMBER
1304	22

DATE MAILED: 01/04/99

Please find below and/or attached an Office communication concerning this application or proceeding.

Commissioner of Patents and Trademarks

Office Action Summary

Application No.	Applicant(s)
08/307,640	Ferguson et al.
Examiner	**Group Art Unit**
Thomas Cunningham	1644

☒ Responsive to communication(s) filed on *Nov 2, 1998*.

☐ This action is **FINAL.**

☐ Since this application is in condition for allowance except for formal matters, **prosecution as to the merits is closed** in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11; 453 O.G. 213.

A shortened statutory period for response to this action is set to expire *3* month(s), or thirty days, whichever is longer, from the mailing date of this communication. Failure to respond within the period for response will cause the application to become abandoned. (35 U.S.C. § 133). Extensions of time may be obtained under the provisions of 37 CFR 1.136(a).

Disposition of Claims

☒ Claim(s) *56-71* is/are pending in the application.

Of the above, claim(s) _____ is/are withdrawn from consideration.

☐ Claim(s) _____ is/are allowed.

☒ Claim(s) *56-71* is/are rejected.

☐ Claim(s) _____ is/are objected to.

☐ Claims _____ are subject to restriction or election requirement.

Application Papers

☐ See the attached Notice of Draftsperson's Patent Drawing Review, PTO-948.

☐ The drawing(s) filed on _____ is/are objected to by the Examiner.

☐ The proposed drawing correction, filed on _____ is ☐approved ☐disapproved.

☐ The specification is objected to by the Examiner.

☐ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. § 119

☐ Acknowledgement is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d).

☐ All ☐ Some* ☐ None of the CERTIFIED copies of the priority documents have been

☐ received.

☐ received in Application No. (Series Code/Serial Number) _____.

☐ received in this national stage application from the International Bureau (PCT Rule 17.2(a)).

*Certified copies not received: _____.

☐ Acknowledgement is made of a claim for domestic priority under 35 U.S.C. § 119(e).

Attachment(s)

☐ Notice of References Cited, PTO-892

☐ Information Disclosure Statement(s), PTO-1449, Paper No(s). _____

☐ Interview Summary, PTO-413

☐ Notice of Draftsperson's Patent Drawing Review, PTO-948

☐ Notice of Informal Patent Application, PTO-152

--- SEE OFFICE ACTION ON THE FOLLOWING PAGES ---

1. The examiner in charge of this application has changed. Please address future correspondence to Examiner Thomas Cunningham in Art Unit 1644.

2. Claims 56-71 are active. Independent claim 56 and claims 57-63 are directed to methods of treating fibrosis comprising providing TGF-β3 to a patient. Independent claim 64 and claims 65-71 are directed to methods of reducing scarring comprising providing TGF-β3 at the wound site. Claims 56 and 64 do not exclude the combination of TGF-β3 with other active factors.

3. A distinguishing property of TGF-β3 is its disclosed ability to induce non-fibrotic growth factor, compared to other forms of TGF-β like TGF-β1 and 2 which may help wounds heal, but which cause fibrosis. This was discussed in the recent interview.. Also, the importance of neutralizing TGFβ1 and TGFβ2, but not TGFβ3 is described in the prior patent to Ferguson et al., U.S. 5,662,904. Limitation of the instant claim language to exclude the presence of fibrotic growth factors such as TGF-β1 and 2 would expedite examination.

4. Claims 57, 58, 60, 65, 66 and 68 (and claims depending from these claims) are rejected under 35 U.S.C. 112, second paragraph as failing to particular point out and distinctly claim the invention. The term "anti-fibrotic agent" is a functionally defined term. It is not defined in terms of structure. Functional definition of a product is not per se fatal if the structure is conventional or can be determined without undue experimentation, In re Gunn, 190 USPQ 402 (CCPA 1976,

In re Donohue, 193 USPQ 136 (CCPA 1977). The structures of the recited "anti-fibrotic agents" are not conventional because the claim language refers to diverse types of molecules alleged to have anti-fibrotic activities, including antibodies, ribozymes and nucleic acids. One with skill in the art would be required to identify each anti-fibrotic agent on a molecule-by-molecule basis as page 1 of the specification indicates that "The mechanism of fibrosis is still not fully understood". Therefore, it would follow that which factors exert fibrotic or antifibrotic activities would not be fully understood either. As indicated on pages 6-7 even molecules within the same structural families, such as TGFβ1, 2 and 3 have different effects on fibrosis.

The Examiner does not dispute that assays could be used to determine which factors are anti-fibrotic under particular assay conditions. However, as there is no predictability a priori as to which molecules would have the recited functional activity of being anti-fibrotic, this term is deemed to be indefinite. Limitation of the claim language to particular structural families of anti-fibrotic agents, such as known anti-fibrotic cytokines or antibodies that bind to and neutralize the activities of particular fibrotic agents (e.g. antibodies to TGFβ1 and 2 as described on page 9 of the specification) would help address this rejection.

5. (Withdrawn) The prior rejection under 35 U.S.C. 112, first paragraph set forth in paragraph 2 of the last office action is withdrawn.

6. (New) Claims 56-71 are rejected under 35 U.S.C. 112, first paragraph as containing subject matter which was not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention.

A. The specification does not provide adequate guidance as to which molecules are anti-fibrotic because it would require undue experimentation to identify such functionally-defined agents--see rejection under 35 U.S.C. 112, second paragraph above. Claims limited to antibodies that specifically neutralize the fibrotic activities of TGFβ1 and TGFβ2, or other known molecules which interfere with the activities of these specific fibrotic growth factors and do not neutralize the anti-fibrotic growth factor activity of TGFβ3 would not be subject to this rejection.

B. The specification does not adequately describe so as to enable ribozymes or oligonucleotides that result in anti-fibrotic activity. For instance, in claims like claims 58 and 66 there is insufficient guidance as to which molecules are "fibrotic growth factors" as whether or not a particular molecule is a growth factor must be determined on a molecule-by-molecule basis and this involves undue experimentation due to the complexity of the cellular milieu and multifunctional nature of TGFβ functional activity which depends on the influences of other growth factors present at the site of wound healing. Claims limited to products which specifically inhibit the fibrotic activities of TGFβ1 and TGFβ2 and do not substantially inhibit the antifibrotic growth factor activity of TGFβ3 would not be subject to this rejection.

C. Assuming arguendo, that the claims are limited to specific and known fibrotic growth factors, such as TGFβ1 and TGFβ2, there is no evidence of record that it is possible to transfect cells with agents such as ribozymes or antisense nucleic acid that suppress expression of such factors. Prima facie, one would expect that cells at the site of a wound would be surrounded or express numerous nucleases that would degrade ribozymes and nucleic acids prior to their uptake by cells expressing fibrotic factors. Thus, such agents would not reasonably be expected to penetrate such cells and diminish expression of the fibrotic factors they express. Evidence that uptake of such products would be expected to occur in healing tissue would obviate this rejection.

D. Assuming arguendo that such products would internalize and modulate intracellular protein expression it would be unpredictable what effects such agents would have on fibrosis and wound healing. Such products would be expected to inhibit both fibrotic and antifibrotic factors so long as they had enough sequence similarity with the oligonucleotide or ribozyme product and thus with one another. For instance, antisense nucleic acids or ribozymes that bind to TGFβ1 and TGFβ2 (that have fibrotic activities) would also be expected to bind to TGFβ3 (which has antifibrotic activity) due to sequence similarities within this family of molecules. Limitation of the claim language to products which do not significantly affect TGFβ3 would help address this rejection.

8. (Withdrawn) The prior rejection under 35 U.S.C. 102(b) set forth in paragraph 4 of the last office action is withdrawn in view of cancellation of the composition claims.

9. Claims 56, 62, 63, 64, and 70-71 are rejected under 35 U.S.C. 103(a) as being unpatentable Cerletti et al, EP 0 433 225 (1990). A similar rejection has been previously set forth in section 5 of the last office action.

Cerletti et al. teach a method for treating wounds using TGFβ like proteins. The compositions disclosed by Cerletti et al. would be expected to comprise TGFβ3 as well as other TGFβ proteins.

Cerletti et al. do not teach the anti-fibrotic growth activity of TGFβ3.

However, the instant claim language does not exclude use of compositions comprising other TGFβ3 in combination with other TGFβ proteins as taught by Cerletti et al. Page 9 of Cerletti et al. discloses different modes and manners of administration of TGFβ like proteins for wound healing.

One with ordinary skill in the medical and pharmaceutical art at the time of invention would have been motivated to use TGFβ like factors comprising TGFβ3 for the purpose of enhancing would healing and would have been motivated to select concentrations and modes of application following page 9 of the cited reference that would have minimized fibrosis at the would site.

Exclusion of fibrotic factors like TGFβ1 and TGFβ2 from the instant claim language would address this rejection. Claims reciting combination of TGFβ3 with an antifibrotic agent are not rejected as Cerletti et al. does not provide motivation for addition of an antifibrotic agent.

10. Any inquiry concerning this communication or earlier communications from the examiner should be directed to Thomas M. Cunningham, Ph.D., J.D., whose telephone number is (703) 308-3968. Dr. Cunningham can generally be reached Monday through Thursday from 7:30AM to 6:00 PM. Any inquiry of a general nature or relating to the status of this application should be directed to the Group receptionist whose telephone number is (703) 308-0196.

TC

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PRIMARY EXAMINER
GROUP 1800